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# Famotidine Use Is Not Associated With 30-day Mortality: A Coarsened Exact Match Study in 7158 Hospitalized Patients With Coronavirus Disease 2019 From a Large Healthcare System

Q4 Samrat Yeramaneni,[1] Pratik Doshi,[1] Kenneth Sands,[2] Mandelin Cooper,[2] Dax Kurbegov,[1] and Gregg Fromell[3]

[1]Sarah Cannon Research Institute, HCA Healthcare, Nashville, Tennessee; [2]Clinical Operations Group, HCA Healthcare, Nashville, Tennessee; [3]HCA Research Institute, HCA Healthcare, Nashville, Tennessee

Previous reports have found that in-hospital famotidine use in coronavirus disease 2019 (COVID-19) patients was associated with reduced risk of death or intubation.[1,2] In 1 of these studies the authors proposed that famotidine inhibits the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease, 3-chymotrypsin-like protease, that is essential for breakdown of the immature SARS-CoV-2 protein particles that contribute to the inflammatory response seen in some COVID-19–infected individuals,[1] which in turn can lead to acute respiratory distress syndrome, multiorgan dysfunction, physiologic deterioration, and death.[3]

In a global pandemic with a lack of US Food and Drug Administration–approved targeted therapeutic agents, identification and repurposing of well-established drugs with a proven track record of safety, affordability, and widespread availability are necessary.[4] The purpose of this study was to evaluate the reported protective effect of famotidine on mortality in hospitalized COVID-19 patients.

## Methods

Refer to Supplementary Methods for complete details. In brief, admitted adults to affiliated hospitals who tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction between February 11, 2020 and May 8, 2020 were included. Exclusion criteria were death or intubation within 48 hours of admission or if famotidine was received >24 hours after admission. The primary outcome was 30-day all-cause mortality. Primary exposure was in-hospital famotidine use, regardless of dose and route, within 24 hours of admission.

To mitigate bias from nonrandomized assignment of treatment, a coarsened exact matching (CEM)[5] technique was used for famotidine users and nonusers on age (by 10-year intervals), sex, race, ethnicity, body mass index, comorbidities, and in-hospital hydroxychloroquine (HCQ) use. A multivariable logistic regression model within the CEM cohort and adjusted for baseline World Health Organization (WHO) severity and use of other medications was performed to evaluate the association between famotidine use and 30-day mortality.

## Results

A total of 8915 patients were assessed for eligibility. Of these, 1441 patients (16.2%) were excluded because of death (1.4%), intubation (5.0%), or famotidine >24 hours after admission (9.8%). Of the 7474 eligible patients, 316 patients were excluded for missing discharge disposition status (0.9%) or >30-day mortality (3.4%), resulting in a final sample of 7158 patients. Of the 7158 patients included in the analysis, 1127 patients (15.7%) were exposed and 6031 patients (84.3%) were unexposed. After CEM of the 1156 patients, 410 patients (35.5%) were exposed and 746 patients (64.5%) were unexposed (Supplementary Figure 1).

### Prematch and Postmatch Characteristics

Overall, 15.7% of patients (n = 1127) received famotidine and 84.3% (n = 6031) did not. Mean age was 57.9 ± 19.3 years, 50.9% were women, 44.6% white, and 25.2% black. Famotidine was used for a median of 6.0 days and at a median cumulative dose of 160 mg (interquartile range, 80-300). Famotidine users were on average 6 years older ($P < .0001$), with higher admission WHO severity ($P < .0001$), higher proportions of comorbid conditions (all $P < .001$), and more likely to receive HCQ, azithromycin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, antibiotics, antivirals, remdesivir, tocilizumab, and steroids (all $P < .001$). Home use of famotidine was documented in 2.5% of famotidine users (n = 181) versus 2.4% of non-famotidine users (n = 170) ($P < .0001$).

The postmatch cohort had 1156 patients (famotidine 35.5% [n = 410] vs non-famotidine 64.5% [n = 746]). The prematch imbalance of 35% in baseline characteristics dropped to 0% after CEM (Supplementary Table 1).

### Thirty-day Mortality

Overall, 687 patients (9.6%) in the prematch cohort and 133 patients (11.5%) in the postmatch cohort died within 30 days of admission. Prematch 30-day mortality was 18.2% of famotidine users versus 8.0% of non-famotidine users ($P < .0001$). Postmatch 30-day mortality was 15.1% of famotidine users versus 9.5% of non-famotidine users ($P = .007$).

***Abbreviations used in this paper:*** **CEM, coarsened exact match; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.**


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The multivariable logistic regression within the matched cohort showed no association between in-hospital famotidine use and 30-day mortality (adjusted odds ratio, 1.59; 95% confidence interval, 0.94–2.71) after adjustment for WHO severity, smoking status, and listed medications. The lack of association remained after controlling for smoking status (Table 1). Secondary analysis, accounting for interaction between in-hospital and at-home famotidine use, showed that patients not using famotidine at home but receiving famotidine in the hospital were at higher risk of 30-day mortality (adjusted odds ratio, 1.77; 95% confidence interval, 1.03–3.03).

**Table 1.** Multivariable Logistic Regression Association Between In-hospital Famotidine Use and 30-day Mortality

| Variables | Adjusted Odds Ratio (95% Confidence Interval) |
|---|---|
| In-hospital famotidine use | |
| World Health Organization Severity Index | |
| Level 2 | Reference |
| Level 3 | 1.55 (0.83–2.87) |
| Level 4 | 2.75 (1.18–6.45) |
| Level 5 | 37.66 (7.45–190.14) |
| Smoking status | |
| Never smoker | Reference |
| Former smoker | 2.05 (1.18–3.56) |
| Current smoker | 2.06 (0.80–5.32) |
| In-hospital medications | |
| Azithromycin use | 0.93 (0.49–1.78) |
| Angiotensin-converting enzyme inhibitor use | 0.69 (0.31–1.55) |
| Angiotensin-receptor blocker use | 0.97 (0.46–2.04) |
| Antiviral use | 1.48 (0.71–3.10) |
| Remdesivir use | 1.24 (0.11–14.19) |
| Tocilizumab use | 2.73 (1.17–6.41) |
| Steroid use | 2.29 (1.34–3.90) |
| Proton pump inhibitor use | 1.49 (0.76–2.95) |
| At-home medications | |
| Famotidine use | 0.49 (0.16–1.52) |
| Proton pump inhibitor use | 1.49 (0.80–2.79) |

World Health Organization Severity Index: level 2, not requiring supplemental oxygen; level 3, requiring low-flow supplemental oxygen; level 4, noninvasive ventilation or high-flow oxygen; level 5, invasive mechanical ventilation or extracorporeal membrane oxygenation. Age, sex, race, ethnicity, body mass index, and comorbidities (coronary artery disease, diabetes mellitus, renal disease, chronic obstructive pulmonary disease, congestive heart failure, and hypertension) were the covariates used in the CEM algorithm.

## Discussion

In this multicenter retrospective study among hospitalized COVID-19 patients, famotidine use within 24 hours of admission did not confer additional risk or benefit to 30-day mortality. In fact, in those not receiving famotidine at home but receiving famotidine in the hospital had a 77% higher risk of 30-day mortality. This significant finding was independent of known adverse outcomes and potential confounders in COVID-19 including age, body mass index, smoking status, comorbid conditions, WHO severity, HCQ use, and other medications.

Freedberg et al[1] reported that famotidine provided a 2-fold reduction in risk of death or intubation for COVID-19 inpatients. Median duration of days and cumulative dose of administration was 5.8 days and 136 mg, respectively, similar to our study. Mather et al[2] reported a similar 2-fold reduction in risk of death or intubation in patients receiving famotidine within ±7 days from COVID-19 screening or hospitalization. These 2 single-center studies had a small cohort of famotidine users (n = 84) compared with our cohort of 476 users. Further, it is unclear whether these 2 studies adjusted for other in-hospital medications. Although Freedberg et al adjusted for traditional confounders including HCQ use, it is unclear whether baseline severity and other in-hospital medications were adjusted. Mather et al adjusted for baseline severity based on NEWS score but did not report on controlling for medications. Given the reports on protective effects of remdesivir[6] and steroids[7] in COVID-19 patients, it is essential to adjust for the effects of medications for valid conclusions.

Limitations of our study include an inability to establish causality and possibility of unmeasured confounding because of the observational design. We did not analyze serum biomarkers or viral load for assessment of anti-inflammatory or antiviral properties. Finally, over 95% of our cohort received low to medium doses, excluding the possibility of evaluating famotidine's effectiveness on mortality at high doses. Despite these limitations, our study captures real-world data from large, multicenter, heterogeneous healthcare institutions allowing generalizability of findings. Matching our comparison groups on 12 covariates reduced an imbalance in baseline characteristics to 0% and adjusted for multiple confounders (n = 12) with association between COVID-19 and mortality.

In summary, our study findings do not support the evidence of in-hospital famotidine use on reduced risk of mortality in COVID-19 patients. Investigation of off-label use of low cost, better tolerated, and widely available drugs in COVID-19 patients is warranted. Until safety and efficacy of these drugs are established by randomized controlled trials,

results from these observational studies should be interpreted with caution.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2020.10.011.

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**Correspondence**
Address correspondence to: Gregg Fromell, MD, HCA Research Institute, 1100 Dr. Martin Luther King Jr. Boulevard, Suite 800, Nashville, TN 37203. e-mail: Gregg.Fromell@HCAHealthcare.com.



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Samrat Yeramaneni, MBBS, PhD (Conceptualization: Equal; Formal analysis: Equal; Investigation: Lead; Methodology: Equal; Writing Equal;ual;l;is: Equal;;Equal; Institute & editing: Lead). Pratik Doshi, MS (Conceptualization: Equal; Data curation: Lead; Formal analysis: Lead; Investigation: Supporting; Methodology: Equal; Validation: Supporting; Visualization: Supporting; Writing thodology: Equal; Validation: S. Kenneth Sands, MD, MPH (Conceptualization: Equal; Investigation: Equal; Methodology: Equal; Project administration: Supporting; Supervision: Lead; Writing t original draft: Supporting; Writing ration: Supporting; Superv. Mandelin Copper, PharmD, BCPS (Conceptualization: Supporting; Investigation: Supporting; Methodology: Supporting; Supervision: Supporting; Writing – review & editing: Equal). Dax Kurbegov, MD (Conceptualization: Supporting; Investigation: Equal; Project administration: Supporting; Writing Investigation: Equal; Pro. Gregg Fromell, MD (Conceptualization: Equal; Investigation: Lead; Methodology: Equal; Project administration: Supporting; Resources: Supporting; Writing tect &ng t editing: Equal).

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# Supplementary Material And Methods

## Study Design and Setting

This study was a retrospective analysis of a consecutive series of patients admitted to HCA Healthcare hospitals between 02/11/2020 and 05/08/2020. During this time period, HCA Healthcare operated 185 locally-managed hospitals ranging in size from 26 to 1,000 beds across 21 states. Facility types included community hospitals, acute care facilities, academic health centers, and large tertiary-referral hospitals. Data for this study was obtained from HCA healthcare's electronic clinical data warehouse. Patients, 18 years or older, who tested positive or presumptive positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) were eligible for the study. Because our hypothesis was aimed at evaluating mild and moderate COVID-19 patients, we excluded patients that were intubated or died within 48 hours of admission.

## Outcomes

The primary outcome was all-cause mortality in the hospital within 30 days of admission.

## Exposures

The primary exposure was in-hospital use of famotidine. Patients who received famotidine, either orally or intravenously, within 24 hours of admission were considered exposed to famotidine. Patients who did not receive famotidine at any time during their hospitalization were considered non-exposed. Patients who received famotidine more than 24 hours after admission were excluded from the analysis. For patients who received famotidine during their hospitalization, total cumulative dose, total number of doses, and total days of exposure during the hospital stay were calculated.

## Covariates

Patient demographic characteristics included age, sex, race, ethnicity, BMI at admission (normal; overweight; obese), and smoking status (never smoker; former smoker; current smoker). Patient severity within 48 hours of admission was assessed using the WHO Severity Index (a six-level ordinal variable). Comorbid conditions included binary indicators for hypertension (HTN), chronic kidney disease (CKD), diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF), and chronic obstructive pulmonary disease (COPD). Other in-hospital medications included binary indicators for hydroxychloroquine (HCQ), azithromycin (AZM), antibiotics, antivirals, remdesivir, systemic corticosteroids, ACE Inhibitors (ACE-I), Angiotensin II Receptor Blockers (ARBs), Proton Pump Inhibitors (PPIs), and tocilizumab use. Patient's home use of famotidine and PPI, recorded at admission, were also included as binary indicators.

## Statistical Analysis

Demographic, clinical, treatment, and outcome characteristics of the patients by famotidine use status are presented as means (SD) or frequencies. Differences in these characteristics between the two groups were assessed using t-test or chi-square test, as appropriate. To mitigate the bias resulting from non-randomized assignment of treatment, a Coarsened Exact Matching (CEM) technique was used to match patients in the comparison group. A 1:n matching, with one famotidine user being matched to many non-famotidine users, on patient age (by 10-year age intervals), sex, race, ethnicity, BMI, all six comorbidities and in-hospital HCQ use was conducted. The matching process assigned weights to all patients in the comparison group, and all further statistical analyses were conducted accounting for these weights.

A multivariable logistic regression model within the matched cohort and adjusted for baseline WHO severity and use of other medications was used to assess the association between famotidine use and 30-day mortality. Additional models were constructed adjusting for the covariates listed above and sequential controlling for smoking status and an interaction effect between in-hospital and at-home famotidine use. Adjusted odds ratio (ORs) and 95% confidence interval (95% CI) for the variables were reported. All statistical analyses were performed using SAS 9.4 (SAS Inc., Cary, NC).

**Supplementary Table 1.** Pre-Match and Post-Match Baseline Characteristics of the Study Cohort

| Baseline characteristics | Pre-Match | | | Post-Match | | |
|---|---|---|---|---|---|---|
| | Famotidine N = 1127 | Non-Famotidine N = 6031 | *P* value | Famotidine N = 410 | Non-Famotidine N = 746 | *P* value |
| Demographics | | | | | | |
| Age in yrs (Mean, SD)* | 63.2 (17.71) | 56.9 (19.42) | <0.0001 | 62.2 (16.86) | 62.1 (16.76) | 0.97 |
| Male*, n (%) | 556 (49.4) | 2959 (49.1) | 0.0675 | 193 (47.1) | 351.2 (47.1) | 1.0 |
| Race*, n (%) | | | 0.0091 | | | 1.0 |
| White | 549 (48.7) | 2642 (43.8) | | 233 (56.8) | 423.9 (56.8) | |
| Black | 306 (27.2) | 1499 (24.9) | | 123 (30.0) | 223.8 (30.0) | |
| Asian | 44 (3.9) | 221 (3.7) | | 5 (1.2) | 9.1 (1.2) | |
| Other | 196 (17.4) | 1,267 (21) | | 49 (11.9) | 89.2 (11.9) | |
| Hispanic*, n (%) | 318 (28.2) | 1608 (26.7) | 0.0297 | 87 (21.2) | 158.3 (21.2) | 1.0 |
| BMI*, n (%) | | | <0.0001 | | | 1.0 |
| Normal | 264 (23.4) | 888 (14.7) | | 85 (20.7) | 154.7 (20.7) | |
| Overweight | 274 (24.3) | 1008 (16.7) | | 118 (28.8) | 214.7 (28.8) | |
| Obese | 397 (35.2) | 1483 (24.6) | | 207 (50.5) | 376.6 (50.5) | |
| Smoking Status, n (%) | | | <0.0001 | | | 0.18 |
| Current Smoker | 48 (4.3) | 195 (3.2) | | 16 (4.1) | 31.3 (4.4) | |
| Former Smoker | 177 (15.7) | 673 (11.2) | | 73 (18.5) | 106.2 (15.0) | |
| Never Smoker | 652 (57.9) | 2567 (42.6) | | 245 (62.2) | 486.7 (68.8) | |
| Comorbidities, n (%) | | | | | | |
| CAD* | 72 (6.4) | 239 (4) | <0.0001 | 7 (1.7) | 12.7 (1.7) | 1.0 |
| DM* | 471 (41.8) | 1639 (27.2) | <0.0001 | 156 (38.1) | 283.8 (38.1) | 1.0 |
| Renal Disease* | 259 (23) | 848 (14.1) | <0.0001 | 69 (16.8) | 125.6 (16.8) | 1.0 |
| COPD* | 321 (28.5) | 1257 (20.8) | <0.0001 | 92 (22.4) | 167.4 (22.4) | 1.0 |
| CHF* | 211 (18.7) | 747 (12.4) | <0.0001 | 36 (8.8) | 65.5 (8.8) | 1.0 |
| Hypertension* | 729 (64.7) | 2809 (46.6) | <0.0001 | 281 (68.5) | 511.3 (68.5) | 1.0 |
| In-Hospital Medication Use, n (%) | | | | | | |
| Hydroxychloroquine* | 654 (58.0) | 1,875 (31.2) | <0.0001 | 256 (62.4) | 465.8 (62.4) | 1.0 |
| ACE Inhibitors | 141 (12.5) | 485 (8.0) | <0.0001 | 50 (12.2) | 104.9 (14.1) | 0.37 |
| ARBs | 103 (9.1) | 385 (6.4) | 0.0008 | 38 (9.3) | 86.4 (11.6) | 0.22 |
| Antibiotics | 1,023 (90.8) | 3747 (62.1) | <0.0001 | 375 (91.5) | 618.3 (82.9) | <0.0001 |
| Azithromycin | 870 (77.2) | 3133 (52) | <0.0001 | 325 (79.3) | 563.2 (75.5) | 0.15 |
| Antivirals | 116 (10.3) | 207 (3.4) | <0.0001 | 56 (13.7) | 48.9 (6.6) | <0.0001 |
| Remdesivir | 11 (1) | 21 (0.4) | 0.0037 | 4 (1) | 3.7 (0.5) | 0.34 |
| Tocilizumab | 63 (5.6) | 101 (1.7) | <0.0001 | 21 (5.1) | 19.1 (2.6) | 0.02 |
| Steroids | 414 (36.7) | 763 (12.7) | <0.0001 | 154 (37.6) | 135.7 (18.2) | <0.0001 |
| PPIs | 129 (11.5) | 940 (15.6) | 0.0003 | 46 (11.2) | 153.5 (20.6) | <0.0001 |
| At-Home Medication Use, n (%) | | | | | | |
| Famotidine Use | 181 (16.1) | 170 (2.8) | <0.0001 | 71 (17.3) | 24.4 (3.3) | <0.0001 |
| PPI use | 275 (24.4) | 1327 (22.0) | 0.0762 | 100 (24.4) | 201.4 (27.0) | 0.33 |

**Supplementary Table 1.** Continued

| Baseline characteristics | Pre-Match Famotidine N = 1127 | Pre-Match Non-Famotidine N = 6031 | Pre-Match *P* value | Post-Match Famotidine N = 410 | Post-Match Non-Famotidine N = 746 | Post-Match *P* value |
|---|---|---|---|---|---|---|
| Other Hospitalization Characteristics, n (%) | | | | | | |
| WHO Severity Index | | | <0.0001 | | | <0.0001 |
| Level 2 | 355 (31.5) | 1596 (26.5) | | 122 (30.3) | 273.8 (37.9) | |
| Level 3 | 541 (48.0) | 2069 (34.3) | | 214 (53.1) | 396.9 (55.0) | |
| Level 4 | 106 (9.4) | 206 (3.4) | | 45 (11.2) | 48.7 (6.8) | |
| Level 5 | 71 (6.3) | 28 (0.5) | | 22 (5.5) | 1.8 (0.3) | |
| Intubated during hospitalization | 96 (8.5) | 124 (2.1) | <0.0001 | 28 (6.8) | 21.4 (2.9) | 0.0014 |
| Received mechanical ventilation during hospitalization | 196 (17.4) | 187 (3.1) | <0.0001 | 63 (15.4) | 27.7 (3.7) | <0.0001 |
| Mortality Outcomes, n (%) | | | | | | |
| 30-Day Mortality | 205 (18.2) | 482 (8) | <0.0001 | 62 (15.1) | 72.9 (9.8) | 0.007 |

NOTE. Cell counts may not add up to 100% due to missing values. CAD, Coronary artery disease; DM, Diabetes mellitus; COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart Failure WHO Severity Index: level 2 - not requiring supplemental oxygen; level 3 - requiring low-flow supplemental oxygen; level 4 - non-invasive ventilation or high-flow oxygen; level 5 – invasive mechanical ventilation or ECMO
*Covariates used in the Coarsened Matching Algorithm